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THE USE OF NON-PEPTIDE NEUROTENSIN RECEPTOR ANTAGONISTS TO EXPLORE THE NEUROBIOLOGICAL ROLES OF NEUROTENSIN

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During the last two decades research on neuropeptides has been extensively carried out. However, the lack of selective tools such as potent agonists and antagonists able to cross the blood brain barrier has hampered the elucidation of the central actions of these neuropeptides and among them the tridecapeptide neurotensin (NT). We describe here the characteristics and some of the central effects of the first potent non-peptide NT antagonist SR 48692, the lead compound of an original chemical family which has been developed by random screening. In vitro, SR 48692 inhibits ^{125}I-NT to the high affinity binding sites (NTR) present in brain tissues from various species including human with IC50 values in the nM range. It also inhibits NT binding to the cloned NTR transfected in CHO cells, an effect which can be related to the blockade by SR 48692 of inositol phosphate formation. Interestingly, this functional receptor is highly glycosylated as demonstrated by means of an anti-peptide antibody against the NT receptor we recently developed. Binding studies using ^{125}I-NT and ^{3}H-SR 48692 with the transfected wild type and deletion mutant NT receptors, indicate that NT and the non-peptide antagonist recognize distinct epitopes on the NT receptor. Binding and autoradiographic studies demonstrate that ^{3}H-SR 48692 recognizes binding sites showing a much lower affinity for NT agonists than those labeled with ^{125}I-NT; however, their brain distribution is very similar to the one of the NTR. We and others previously demonstrated a close relationship between NT and central dopaminergic systems and suggested that NT may be involved in neurological and neural disorders associated with altered dopaminergic (DA) transmission. We observed both in animals and in human that NTR were present in regions rich in both DA cell bodies (midbrain) and terminals (basal ganglia) and that the binding of ^{125}I-NT was inhibited by SR 48692 in those regions in the nM range. SR 48692 which has no agonist effect by itself antagonizes NT potentiation of K^{+}-induced ^{3}H-DA release. In vivo, SR 48692 prevents retrograde axonal transport of NT in rat nigrostriatal system as well as NT-induced hypomotility, but fails to block NT-induced hypothermia and analgesia in mouse and rat. Furthermore, it potentiates neuroleptic-induced release of DA in the mesolimbic system. Chronic treatment with SR 48692 is able to induce an up-regulation of NTR and to reduce the activity of the hypothalamo-pituitary-adrenal axis. It can thus be possible to use such antagonists as tools to explore the physiology of NT and to reveal yet unknown NT receptor subtypes.